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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/743,395 | 02/07/2001 | Bernd Dorken | 101195-38 | 2292 |

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| EXAMINER | |
|---|---|
| VOGEL, NANCY S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | 18 |

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/743,395 | DORKEN ET AL. | |
| | Examiner | Art Unit | |
| | Nancy Vogel | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with th corr spondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/7/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 15-26 are pending. Receipt of the amendment submitted 11/17/03 is acknowledged.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/03 has been entered.

### *Specification*

The disclosure is objected to because of the following informalities:

In the figure legend for Figure 3, there are still two sets of empty parenthesis (lines 5 and 6).

Appropriate correction is required.

### *Drawings*

The drawings are objected to because German text remains in Figures 1 and 2. A proposed drawing correction or corrected drawings are required in reply to the Office

action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

### *Claim Objections*

Claim 24 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The recitation of "tumorigenic or non-tumorigenic" encompasses all cells, and does not further limit the recitation in claim 15 of "cell".

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-18, 21, 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Nabel et al. (WO 97/11720) (previously cited by the Examiner in Paper Nos. 7 and 10, mailed 5/21/01, and 4/23/02.

This rejection is maintained essentially for the reasons set forth in the previous office action, applied there to now cancelled claims 1-3, 5, and 9-11, but still applicable to the newly submitted claims. To recapitulate, Nabel et al. teach a method comprising

the steps of preparing a transfected mammalian cell by transferring into said cell a first polynucleotide comprising a promoter operably linked to the coding sequence of p21, and a second polynucleotide comprising a promoter operably linked to a coding sequence (see pages 3-6 and 11-12, and claim 10). The polynucleotides may be an adenoviral vector (page 6). Nabel et al. disclose the method both in vitro and in vivo (see page 12-15 and pages 17-25, and claims). Nabel et al. disclose the method in a primary cell line or established cell line, including tumorigenic and non-tumorigenic cells (page 12-13, page 22-23). Nabel disclose the method in a human cell, or any mammal, in vivo (see claims and page 11, lines 17-18). Absent evidence to the contrary, it is assumed that a method comprising the same steps as recited in the claimed method will achieve the same purpose, by the same mechanisms.

Claims 15, 19, 20, 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Mudryj et al. (US Pat. No. 5,705,350) (previously cited by the Examiner).

Mudryj et al. teach a method comprising transferring into an established mammalian cell line (NIH3T3) a vector comprising the p21 coding sequence operatively linked to a promoter and a separate vector comprising a promoter operably linked to a coding sequence (see col. 10, Ex. 12), and maintaining the transfected mammalian cell under conditions conducive to synthesizing p21. The mammalian cell is transfected in vitro. Absent evidence to the contrary, it is assumed that a method comprising the same steps as recited in the claimed method will achieve the same purpose, by the same mechanisms.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection : the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The present claims are very broad. Claim 15 encompasses a method for improving the stable transfer of any genetic material into any target cells comprising transfecting any cell with a polynucleotide comprising a cDNA for p21 and a second polynucleotide comprising any coding sequence.

The nature of the invention is a method for improving the stable transfer of genetic material into mammalian cells comprising transferring into a mammalian cell the p21 gene and a gene of interest.

An analysis of the prior art as of the effective filing date of the present application shows several examples of studies of overexpression of p21 in mammalian cells. Common results of overexpression of p21 include growth inhibition and cell cycle arrest. See Kokunai et al (Int. J. Cancer 1998 75 :643-648) (previously cited by the Examiner in Paper Nos. 7 and 10, mailed 5/21/01 and 4/23/02). Notably, however, other effects of overexpression appear to be cell-type dependent. For instance, overexpression of p21 in GB-1 cells (a human glioblastoma cell line) inhibited DNA synthesis and did not induce apoptosis. Overexpression of p21 in U87-MG cells, another human glioblastoma cell line, however, did result in apoptosis. See Kondo et al (Oncogene 1996 13: 1279-1285 previously cited by the Examiner in Paper Nos. 7 and 10, mailed 5/21/01 and 4/23/02).

The relative skill of those in the art of genetic transformation of mammalian cells is high.

The area of the invention is unpredictable. As discussed above, while there are some effects of p21 overexpression in a give n cell that are common (growth inhibition and cell cycle arrest), there are others, including differentiation and apoptosis, which are not common and appear to be cell-type specific and are therefore not predictable.

The present specification provides no direction or guidance to support the claimed invention. The specification teaches that any mammalian cell may be used,

any vector (viral or non-viral) and any selected gene; adenovirus-based vectors are preferred. There are no teachings on which mammalian cells may be appropriate targets and which are not, or any preferences among the huge number of possibilities for the chosen gene.

The working examples disclosed use LoVo cells as the target cell. The cells were mock infected with buffer, infected with an adenovirus vector comprising a human alpha-1 antitrypsin gene, or with an adenovirus vector comprising a p21 gene. No cell was transfected with both p21 and a selected gene, on separate vectors, and there is no direct evidence that such a transfection leads to improvement of stable transfer of genetic material. Thus, the working examples do not encompass the invention as claimed.

The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the specification to teach how to use the claimed method. In order to determine how to use the method, one would have to determine what combination of mammalian cell type, vector type and selected gene, expressed with p21, will be successful in the claimed method. Since the number of permutations for these combinations is large, it would require a large quantity of trial and error experimentation by the skilled artisan.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method

for improving the stable transfer of genetic material into mammalian cells comprising transfecting any cell, or any rodent cell, (claim 22), or any human cell (claim 23) with a polynucleotide comprising a cDNA for p21 and a second polynucleotide comprising any selected gene whereby stable transfer is improved.

Claims 20, 22, 24, 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed: "wherein the mammalian cell is an established cell line or a primary culture" (claim 20); "wherein the mammalian cell is a rodent cell" (claim 22); "wherein the mammalian cell is tumorigenic or non-tumorigenic" (claim 24)' "wherein the improved stability results from the p21-mediated inhibition of cytoxicity" (claim 26). This a new matter rejection. The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned limitations, as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15, and by dependence claims 16-26, are vague and indefinite in reciting "improving the stable transfer". "Improving" is a relative term; over what is this method an improvement?

## *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 6:30 - 3:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ntv

TERRY MCKELVEY
PRIMARY EXAMINER